Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 29-37, 44, 45, 47, 48, and 61-77 are pending in the application, with claim 29 being the independent claim. New claims 61-77 are sought to be added. Support for the new claims is found, *inter alia*, at page 2, lines 20 to page 3, line 2; page 6, lines 7 to page 7, line 2; page 7, lines 18-23; page 8, lines 2-4; page 8, line 31 to page 9, line 12; page 18, line 20 to page 19, line 18; page 21, line 14 to page 22, line 12; page 25, line 14 to page 26, line 20; and page 27, lines 6-24; at Figures 12-16; in the original claims and throughout the Specification (all page numbers herein are based on priority application PCT/KR2003/001400, Publ. No. WO 2004/007734). These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Statement of Substance of the Interview

Further to the Interview Summary mailed on July 3, 2008, Applicants submit the following Statement of the Substance of the Interview in accordance with M.P.E.P. § 713.04. Applicants thank Examiners Kevin Hill and Janice Li for their time in participating in the interview of June 26, 2008, to discuss the outstanding office action with the undersigned attorney. During the interview, Applicants' representative and the Examiners discussed the §112 and §103 rejections in the outstanding Office Action and possible claim amendments.

Objection to the Claims

Claim 29 has been objected to because of the comma (line 3) after Her-2/neu. Office Action, page 3. Applicants have amended claim 29, including removing the comma. Thus, the objection has been rendered moot.

Applicants respectfully request that the objection be withdrawn.

Indefiniteness Rejection under 35 U.S.C. § 112, Second Paragraph

Claims 47-60 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Office Action, page 3. Specifically, the Examiner asserts that claims 47, 49, 52, 55, and 59 (and dependent claims) are vague and indefinite in that no step(s) in the claimed method refers back to or recapitulates the preamble of the claim.

Claims 49-60 have been cancelled. Thus, the rejection has been rendered moot with regard to these claims. Currently pending claim 47 has been amended to recite, "wherein said mammal develops an immune response to said Her2/neu protein thereby preventing or treating a Her-2/neu-over-expressing human cancer."

Accordingly, Applicants believe that the rejection under 35 U.S.C. § 112, second paragraph, has been fully accommodated or rendered moot, and respectfully request that the rejection be withdrawn.

Enablement Rejection under 35 U.S.C. § 112, First Paragraph

Claims 47, 48, and 49-60 have been rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Office Action, pages 4 and 8. The Examiner alleges that the specification is not enabling for the disclosed method of preventing or treating mammalian subjects, including humans. Office Action, page 9. Applicants respectfully disagree.

Specifically, the Examiner alleges that the specification fails to provide any guidance as to how an artisan would have dealt with the art-recognized limitations of the claimed methods. Office Action, page 8. The Examiner alleges that the art recognizes a lack of standards in animal models; unpredictability regarding gene therapy and DNA vaccine technologies to elicit a specific immune response sufficient to achieve a clinically-relevant therapeutic outcome; and although proven to be quite effective in rodents, DNA-based vaccines have generally performed poorly in both non-human primate studies as well as in human clinical trials. Office Action, page 15. The Examiner also asserts that the substantive issue is that the instant specification does not enable the artisan to use the inventive DNA vaccine plasmids in the claimed methods of treating an enormous genus of mammals, including humans. Office Action, page 16.

Claims 49-60 have been cancelled. Thus, the rejection has been rendered moot with regard to these claims. With regard to claims 47, 48 and new claims 61-77, Applicants respectfully assert that the full scope of the currently pending claims is enabled.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: the breadth of the claims; the nature of the invention; the state of the

prior art; the level of one of ordinary skill; the level of predictability in the art; the amount of direction provided by the inventor; the existence of working examples; and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), *see also* M.P.E.P. §2164.01(a).

Applicants assert that the claims as amended satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph, because the claimed invention is enabled so that any person skilled in the art can make and use the invention without undue experimentation. In support of this conclusion, the *In re Wands* factors are discussed below.

Breadth of the Claims

The Examiner alleges that the method claim is broad for encompassing treatment methods as applied to humans, wherein Applicant contemplates an enormous genus of DNA vaccine formulations and administration means. Office action, pages 5 and 9-10. Applicants disagree and contend that the method and composition claims of the current invention are not unreasonably broad. Where the art recognizes that standard modes of administration are known and contemplated then 35 U.S.C. §112 is satisfied. *See* M.P.E.P. §2164.01(c). The current specification provides examples of DNA vaccine formulations for administration in an animal model. The specification also provides guidance for administration, formulation and dosage of the DNA vaccines of the invention in humans, which a person of ordinary skill would find sufficient to make and use the claimed invention. *See, e.g.*, Specification at page 10, line 7 to page 11, line 16. While ample support is provided for many modes of administration, in an effort to advance prosecution and without acquiescence to Examiner's argument, claim 47 is amended to specify intramuscular administration. The methods of new

claims 61-77 are also directed to intramuscular administration. Thus, the method claims as currently amended are not unreasonably broad.

The Examiner also alleges that with respect to the DNA vaccine composition, the breadth of the claim is exceptionally large for encompassing a genus of structurally distinct nucleic acid compositions encoding structurally and biologically distinct polypeptides for use as a DNA vaccine for the treatment and/or prevention of Her-2/neu-over-expressing cancers, including carcinoma of the breast, prostate, ovary, uterus, stomach and adenocarcinoma of the lung. Office Action, pages 5 and 11-12. In an effort to advance prosecution and without acquiescence to Examiner's argument, claim 29 is amended to specify a pharmaceutical composition comprising a C-terminally truncated human Her-2/neu protein, said protein *consisting* of a signal peptide, the entire extracellular domain and transmembrane domain of Her-2/neu or a signal peptide and the entire extracellular domain of Her-2/neu; and an adjuvant. Thus, the pharmaceutical compositions and methods of the claimed invention are not exceptionally large or unreasonably broad for treating the well defined and readily identifiable group of Her-2/neu over-expressing human cancers.

State of the Prior Art, Level of One of Ordinary Skill in the Art and Level of Predictability in the Art

The Examiner notes that the relevant art of the instant invention is DNA vaccines, wherein the level of skill for the ordinary artisan is high. Office Action, page 5. The Examiner asserts that the art recognized significant unpredictability regarding the design of any Her-2/neu DNA vaccine, with or without combined administration of nucleic acids encoding a cytokine, to reliably prevent or treat an enormous genus of etiologically and

pathologically distinct tumors in an enormous genus of mammalian organisms, including mice and humans. Office Action, page 7.

Applicants herein provide evidence to support that one skilled in the art would be able to make and use the full scope of the claimed invention using the application as a guide, without undue experimentation. Applicants respectfully point out that such evidence need not be conclusive but merely convincing to one of skill in the art. *See* M.P.E.P. §2164.05. Applicants provide herewith as **Exhibit A** the Declaration under 37 C.F.R. § 1.132 of Chang-Yuil Kang, Ph.D., along with accompanying **Exhibits AA-AQ** cited therein. Dr. Kang is an expert in the field of vaccine research and development and immunology. Dr. Kang currently is a professor at Seoul National University and was asked to evaluate the state of the art and level of predictability in the art around the time of filing of the parent application of which the present application claims benefit. In particular, Dr. Kang explains that the animal model used to test the DNA vaccine of the current invention was commonly used in the art in preclinical studies of vaccines, and was viewed as reasonably predictive of similar results in mammals, including humans. *See* Kang Declaration at paragraph 6.

Existence of Working Examples and Amount of Direction Provided by Inventor

The Examiner further alleges that the mouse model used for testing the experimental DNA vaccines of the invention may not be representative for the human scenario. Office Action, pages 5-7 and 10-12. Applicants disagree and contend that the animal model example in the specification constitutes a working example. An animal model example, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method of the invention. *See* M.P.E.P. §2164.02. "Correlation" depends on the state of the prior art, and a rigorous or an invariable exact correlation is *not* required. *Id.* Even if

the examiner has evidence that the model does not correlate, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as *reasonably* correlating. *Id.* Applicants contend that the mouse model of the invention is reasonably predictive of similar results in mammals, including humans. Applicants draw the Examiner's attention to the following points: (1) the animal model used to test the DNA vaccine of the current invention was commonly used in the art in preclinical studies of vaccines, and was viewed as reasonably predictive of similar results in mammals, including humans and (2) post-filing art shows that the teachings of the present application were reasonably predictive that the Her-2/neu DNA vaccine would be effective for preventing/treating spontaneous tumors and that DNA vaccines originally tested in mouse models have been shown to be safe and effective in mammals, including humans.

As evidence related to points (1) and (2) above, Applicants provide herewith as **Exhibit A** the Declaration under 37 C.F.R. § 1.132 of Chang-Yuil Kang, Ph.D., along with accompanying **Exhibits AA-AQ** cited therein. With respect to point (1), Dr. Kang explains in detail why one of ordinary skill in the art would have recognized that the animal model described in the current invention was reasonably predictive of similar results in humans. The use of mice injected with cancer cells was a commonly used preclinical model for testing cancer vaccines, including protein and DNA vaccines, as of the effective priority date of the present application. *See* Kang Declaration at paragraph 7. In particular, Dr. Kang describes three publications where, like the disclosure of the current application, cancer vaccines were tested in mice injected with CT26 cells expressing a tumor associated gene. Positive results in this mouse model provided support for human clinical trials. *See, e.g.*, Conry *et al.*, "A Carcinoembryonic Antigen Polynucleotide Vaccine has in vivo Tumor Activity" *Gene Therapy 2*: 59-65 (1995) (**Exhibit AB**).

As discussed by Dr. Kang, the BALB/c-Her2-CT26 mouse model is particularly useful for predicting results in humans because it is used to test the preventative and therapeutic effects of the Her-2/neu DNA vaccines. As of the priority date of the current invention, it was known that induction of anti-tumor immunity, in part, involves CTL responses. *See, e.g.*, Irvine *et al.*, "Cytokine Enhancement of DNA Immunization Leads to Effective Treatment of Established Pulmonary Metastases" *J Immunol. 156*(1): 238–245 (1996) (**Exhibit AD**). Several studies had shown that antibody and CTL responses in mice could be recapitulated in other mammals, including humans. *See*, e.g., Wang *et al.*, "Induction of Antigen-Specific Cytotoxic T Lymphocytes in Humans by a Malaria DNA Vaccine" *Science 282*:476-480 (1998) (**Exhibit AF**) and Boyer et al., "Protection of Chimpanzees from High-dose Heterologous HIV-1 Challenge by DNA Vaccination" *Nature Med. 3*(5):526-532 (1997) (**Exhibit AH**).

In Dr. Kang's opinion, persons of ordinary skill in the art would have considered the induction of CTL and antibody responses in the animal model used in the current invention a reasonable indicator of anti-tumor immunity in humans. *See* Kang Declaration at paragraph 9. The present application provides working examples where i.m. administration of the claimed truncated Her-2/neu DNA vaccine was effective at inducing CTL and antibody responses in mice both pre-injection and post-injection with human Her-2/neu expressing murine tumor cells (Her-2-CT26). See Specification at page 6, line 7 to page 7, line 2; page 7, lines 18-23; page 8, lines 2-4, and page 18, line 20 to page 19, line 18. In addition, these results correlated with increased anti-tumor immunity and survival in mice challenged with Her-2-CT26 cancer cells. *See* Specification at page 19, line 20 to page 20, line 9; page 21, line 14 to page 22, line 12; and page 23, lines 7-31. Thus, a person of ordinary skill in the art would have viewed the results described in the specification as reasonably predictive of

similar results in other mammals, including humans. *See* Kang Declaration at paragraphs 8 and 9.

With respect to point (2), Dr. Kang discusses post-filing references which show that the teachings of the present application indeed *were* reasonably predictive that the Her-2/neu DNA vaccine would be effective for preventing/treating spontaneous tumors. For example, post-filing art discussed in Dr. Kang's Declaration show other mouse models which indicated that Her-2/neu DNA vaccines were likely to predict safe and effective results in humans. *See* Smorlesi *et al.*, "Evaluation of Different Plasmid DNA Delivery Systems for Immunization against HER2/neu in a Transgenic Murine Model of Mammary Carcinoma" *Vaccine 24*: 1766-1775 (2006) ("Smorlesi"). Smorlesi, previously cited by the Examiner in the Office Action dated April 22, 2008, describes a Her-2/neu DNA vaccine which was used to treat spontaneous tumor formation in a Her-2/neu transgenic mouse model. Specifically, the DNA plasmid vaccine comprised a nucleotide sequence encoding an extracellular and transmembrane region of Her-2/neu under the control of the CMV early promoter. *Id.* at 1767. Smorlesi describes the effect of the DNA vaccine on the incidence and the growth of spontaneous tumors in FBVneu-T transgenic mice. *Id.* at 1769, Figure 1. In Dr. Kang's opinion, these data show that the animal models in the present application, *e.g.*, decreased tumor formation in mice injected with Her-2/neu expressing cancer cells, were predictive that the Her-2/neu DNA vaccine would be effective for preventing/treating spontaneous tumors. *See* Kang Declaration at paragraph 16.

In addition, DNA-based vaccines were well developed, or in progress, for a variety of disease conditions at the time of the invention. For example, Malaria and HIV-1 DNA

vaccines had been tested in rodent models and subsequently shown to elicit immune responses in humans. *See* Kang Declaration at paragraph 13.

The Examiner also asserts that the prevention and treatment of humans related to Her-2/neu-over-expressing cancers is "an inoperative embodiment." Office Action, page 15. While Applicants vigorously disagree with the Examiner's characterization of the specification as including "inoperative embodiments," the Applicants respectfully point out that the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling). *See* M.P.E.P. §2164.08(b).

As discussed above and in Dr. Kang's Declaration, the inventors provided sufficient direction to allow a person of ordinary skill in the art to make and use the claimed invention. For example, the specific DNA vaccine constructs of the invention were tested in an animal model that was reasonably predictive of similar results in other mammals, including humans. The specification provides guidance for administration, formulation and dosage of the plasmid constructs, which a person of ordinary skill would find sufficient to make and use the claimed invention. *See* Kang Declaration at paragraph 11. Specifically, the specification describes a suitable dosage range from about 0.01 to 10 mg/kg/day, and further describes dosing to include a multiple dose schedule. *See, e.g.*, Specification at page 10, line 7 to page 11, line 16. Thus, the methods of the claimed invention require expenditure of no more effort than is normally required in the art for making and using the claimed Her-2/neu DNA vaccine

composition for prevention or treatment of a Her-2/neu-overexpressing cancer in a mammal, including a human.

Quantity of Any Necessary Experimentation to Make or Use the Invention

As evidenced by clinical trials currently in progress, the quantity of any necessary experimentation to make or use the invention is not unreasonable. For example, Dr. Kang discusses clinical trials in which DNA vaccines, including Her-2/neu DNA vaccines, are currently being tested in humans for cancer treatment, as was described in the specification of the instant application. Based on preclinical results, several Her-2 DNA vaccine trials have been initiated. *See* Wei *et al.*, "The "A, B and C" of Her-2 DNA Vaccine Development," *Cancer Immunol. Immunother.* February 14, 2008 [Epublication ahead of print] (**Exhibit AP**). In particular, a pilot clinical trial testing pVAX-E2A, conducted at the Karolinska Institute, Stockholm, Sweden, in stage IV breast cancer patients is underway. The trial is titled "Vaccine immunization with nucleic acid coding for the gene Her-2/neu together with low doses GM-CSF (Leucomax*) and IL-2 (Proleukin*) as adjuvant in patients with metastatic breast carcinoma." *Id.* The study results show thus far no adverse effects. *Id.* Thus, results shown in the specification of the current invention using the truncated Her-2/neu DNA construct and cytokine adjuvant of the invention to treat mice exposed to Her-2/neu tumor cells provided a basis for clinical trails in humans that could be performed without undue burden by a person of ordinary skill in the art. *See* Kang Declaration at paragraph 18.

In another on-going phase I study for a Her-2 DNA vaccine, the DNA vaccine is being administered intramuscularly as a series of 5 injections (2.5 mg/injection), every other week over a 94 week duration. *See* ClinicalTrials.gov Identifier: NCT00647114 at

ClinicalTrials.gov (last visited, July 11, 2008) **(Exhibit AQ)**. The i.m. administration and dosage currently being tested in the NCT00647114 clinical trial are similar to the administration and dosage described in the specification for the truncated Her-2/neu plasmid constructs of the current invention. *See* Specification at page 10, line 7 to page 11, line 28. Thus, the on-going Her-2 DNA vaccine clinical trials show that the specification of the current invention was reasonably predictive of therapeutic and preventative methods and uses of the claimed invention in humans, and the specification provides guidance for a person of ordinary skill in the art to use the methods of the claimed invention without undue burden.

The method claims as currently amended are directed to a methods comprising *intramuscularly* administering an effective amount of a pharmaceutical composition that includes a nucleotide sequence encoding a C-terminally truncated human Her-2/neu protein, said protein *consisting* of a signal peptide, the entire extracellular domain and transmembrane domain of Her-2/neu or a signal peptide and the entire extracellular domain of Her-2/neu; and an *adjuvant*. The currently amended claims are not unreasonably broad and are supported by the disclosure in the specification, including working examples. In particular, the animal model used to test the DNA vaccine of the current invention was commonly used in the art in preclinical studies of vaccines, and was viewed as reasonably predictive of similar results in mammals, including humans. The specification, in combination with knowledge in the art at the time of filing, teach one of ordinary skill in the art how to make and use the claimed invention without undue experimentation. This conclusion is further supported by results described in the post-filing art where the compositions and methods used are similar to those disclosed in the current specification. The discussion of the *In Re Wands factors* above, shows that the amended claims of the current invention are fully enabled. Accordingly, Applicants believe that the rejections under 35 U.S.C. § 112, first paragraph, have been

properly traversed, fully accommodated or rendered moot, and respectfully request that the rejections be withdrawn.

Obviousness Rejection under 35 U.S.C. § 103

Piechocki, Erickson, Chen, Lee 1, and Lee 2, as evidenced by Bocchia

The Examiner has rejected claims 29-30, 32-39, and 41-60 under 35 U.S.C. § 103(a) as being obvious over Piechocki *et al.* (J. Immunol. 167: 3367-3374, 2001, hereinafter "Piechocki") in view of Erickson *et al.* (WO 01/00244), Lee *et al.* (J. Virol. 72(10):8430-8436, 1998, hereinafter "Lee 2"), Lee *et al.* (Biochem. Biophys. Res. Comm. 272(1): 230-235, 2000, hereinafter "Lee 1"), and Chen *et al.* (Cancer Res. 58:1965-1971, 1998, hereinafter "Chen"), as evidenced by Bocchia *et al.* (Haematologica 85: 1172-1206, 2000, hereinafter "Bocchia"). Office Action, page 17.

More specifically, the Examiner asserts that Piechocki teaches a plasmid DNA vaccine comprising a nucleotide sequence encoding a truncated human Her-2/neu polypeptide, said polypeptide consisting of an extracellular domain, specifically the amino terminal amino acids 1-505 of the mature human Her-2/neu extracellular domain. Office Action, page 17. Further, the Examiner asserts that Piechocki teaches a method of preventing or treating cancer and inducing anti-tumor immunity. Office Action, page 18. The Examiner notes that Piechocki does not teach the truncated Her-2/neu polypeptide to be encoded by a nucleic acid sequence comprising SEQ ID NO:2. However, the Examiner alleges that Erickson demonstrates that the sequence of human Her-2/neu having 100% identity to SEQ ID NO:2 was known in the art. The Examiner asserts that although Piechocki does not teach use of a pTV2 vector, Lee 2 teaches the eukaryotic expression vector pTV2 to express a

single gene of interest, specifically GM-CSF, Elt or E2t, or a bicistronic expression plasmid to express a gene of interest in combination with GM-CSF. Office Action, pages 17-18. The Examiner further asserts that although Piechocki does not teach use of a pCK vector, Lee 1 teaches the construction of a pCK expression plasmid that is able to drive high levels of gene expression *in vivo* for therapeutic use. Office Action, page 18. The Examiner alleges that Chen teaches the ability of the ordinary artisan to express subdomains of Her-2/neu, specifically the extracellular domain ($pNeu_E$) or the extracellular domain and transmembrane domain ($pNeu_{TM}$). Office Action, page 19.

Claims 37-39, 41-43, 46, and 49-60 have been cancelled. Insofar that the rejection applies to the currently pending claims 29-30, 32-36, 44, 45, 47, 48, and 61-77, Applicants respectfully traverse this rejection.

The factors to be considered under 35 U.S.C. § 103(a) are the scope and content of the prior art; the differences between the prior art and the claims at issue; and the level of ordinary skill in the pertinent art. *See Graham v. John Deere*, 86 S.Ct. 684 (1966); M.P.E.P. §2141; *KSR International Co v. Teleflex Inc.*, 127 S.Ct. 1727 (2007). The Office published Examination Guidelines to aid Examiners in formulating obviousness rejections. *See* Examination Guidelines for Determining Obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in *KSR International v. Teleflex Inc.* Fed. Reg. Vol. 72, pp. 57526 to 57535 (October 10, 2007), hereinafter "the Examination Guidelines." Seven rationales are suggested by which obviousness may be found, *e.g.*, by combining elements in the art or substituting one known element for another. As a common thread through all the rationales, the Examiner must establish on the record that a person of ordinary skill in the art would have recognized that the results of the combination or substitution were *predictable*. *Id.*, *e.g.*, at

57529. Applicants also note that where the pathway to the invention, in retrospect, may seem to follow logical steps to produce the inventive properties, the Examiner cannot discount the inventor's insights, willingness to confront and overcome obstacles, and even serendipity, at the time of invention. *See Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, No. 2007-1223, page 10, slip op. (Fed. Cir. March 31, 2008).

As currently amended, claims 29-30, 32-36, 44, 45, 47, 48, and 61-77 are directed to compositions and methods related to a pharmaceutical composition comprising (i) a pTV2 or pCK plasmid construct comprising a promoter operably linked to a nucleotide sequence encoding a C-terminally truncated *human* Her-2/neu protein *consisting* of a signal peptide, the *entire* extracellular domain and transmembrane domain of Her-2/neu or a signal peptide and the *entire* extracellular domain of Her-2/neu; and (ii) an *adjuvant*. Ascertaining the differences between the prior art and the claims at issue requires interpreting the claim language, and considering both the invention and the prior art references as a whole. *See* M.P.E.P. §2141.02. Applicants assert that when the invention and the prior art references are considered as a whole, a person of ordinary skill in the art would not have predictably arrived at the current invention by combination or substitution of the references cited by the Examiner.

Piechocki describes a pCMV plasmid with a nucleotide sequence encoding a secreted Her-2/neu (secE2) that includes the ER signal peptide (aa 1-21) and N-terminal amino acids 1-505 (encoding most of the ECD) of the mature protein for use as a DNA vaccine. Piechocki at page 3368. Unlike the claimed invention, the Piechocki construct does not contain the *entire* extracellular domain, nor does it include the *entire* extracellular domain and transmembrane domain. At the time of Applicants' invention, it was *unknown* which

Her-2/neu epitopes were likely to provide the best tumor rejection in animal models and humans. *See* Piechocki at 3368. As stated in Piechocki, "there is still some debate as to which epitopes are most important for tumor rejection in murine and human models and the way in which to best present these Ags to the immune system for effective priming." *Id.*

The current specification discloses that in mice immunized with the DNA plasmids of the invention, both Her-2/neu-specific antibody responses and Her-2/neu-specific CTL responses were induced. *See* Specification at page 18, line 20 to page 19, line 18; page 24, line 23 to page 25, line 12. Although Piechocki discloses that secE2 induced antibody response and antitumor activity, secE2 did *not* induce significant CTL response when compared with E2. *See* Piechocki at 3373. The authors note that CTL are critical effectors even if antibodies have direct effect. *Id.* As of the priority date of the current invention, it was also known that induction of anti-tumor immunity, in part, involves CTL responses. *See* Irvine at 238. In order to achieve elevated CTL activity, Piechocki vaccinated mice with a combination of secE2 and a second Her-2/neu construct, cytE2. *Id.* The cytE2 construct included a truncated endoplasmic reticulum (ER) domain, but intact intracellular domain, extracellular domain and transmembrane domain. Therefore unlike the construct of the current invention, cytE2 is not C-terminally truncated and lacks a signal peptide. Piechocki discloses that by vaccination with the combination of secE2 and cytE2, which contains the entire repertoire of ErbB-2 epitopes, all epitopes can be presented *in vivo*, and thereby provide a greater chance of inducing functional CTL. *Id.* Piechocki *et al.* predicts that covaccination with DNA encoding all Her-2/neu epitopes is needed to achieve elevated CTL activity and complete tumor protection. *Id.* In contrast, the current specification shows that the DNA vaccine of the claimed invention achieved CTL induction and complete tumor protection, as well as inhibition of tumor growth after injection, *without* all epitopes of Her-

2/neu. *See* Specification at page 26, line 17 to page 27, lines 23; Figures 13c, 13d, 15c. In particular, mice treated with pCK_{TM} + pCK_{TM}-GMCSF had a 100% survival rate after tumor challenge. *See* Figure 13c. Further, mice exposed to tumor cells and then treated with bicistronic plasmids, pCK_{TM}-IL18, pCK_{TM}-Flt3L and pCK_{TM}-GMCSF, of the invention showed complete inhibition of tumor growth. *See* Figure 15c. Applicants point out that the prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984), *see also* M.P.E.P. §2141.02. Thus, when viewed as a whole, Piechocki teaches away from use of a pharmaceutical composition comprising a C-terminally truncated Her-2/neu construct, *without* presentation of the other Her-2/neu epitopes, for prevention or treatment of cancer as described in the claimed invention.

Further, the claims as currently amended include an *adjuvant*. Piechocki does not describe use of an adjuvant. In particular, Piechocki does not describe a pharmaceutical composition comprising a Her-2/neu DNA vaccine in combination with a cytokine, as described in the current invention. As pointed out by the Examiner, the art recognized significant unpredictability regarding the design of any Her-2/neu DNA vaccine, with or without combined administration of nucleic acids encoding a cytokine, to reliably prevent or treat mammalian organisms, including mice and humans. *See* Office Action, page 7. The preventive and therapeutic anti-tumor activities of the truncated Her-2/neu DNA plasmids of the invention were promoted by co-injection of DNA encoding a cytokine as an adjuvant (either on a separate plasmid or bicistronic plasmid), resulting in decreased tumor growth and prolonged survival of vaccinated mice. *See* Specification at page 26, lines 15-17; page 27, lines 13-24. Thus, it was not predictable based on Piechocki in combination with the other

references cited by the Examiner that the pharmaceutical composition of the current invention would be effective for preventing or treating Her-2/neu-expressing cancers.

Therefore, Piechocki does not teach a person of ordinary skill in the art the specific pharmaceutical composition of the amended claims which specify a C-terminally truncated human Her-2/neu protein, said protein *consisting* of a signal peptide, the *entire* extracellular domain and transmembrane domain of Her-2/neu or a signal peptide and the *entire* extracellular domain of Her-2/neu. Nor does Piechocki predict that the pharmaceutical composition of the claimed invention that includes the C-terminally truncated Her-2/neu and an adjuvant would be likely to provide sufficient antibody *and* CTL response to support use as an effective preventative and therapeutic DNA vaccine. On the other hand, the current specification discloses properties of the pharmaceutical compositions of the current invention that were unpredictably superior to the secE2 construct disclosed in Piechocki.

Contrary to Examiner's assertion, Erickson does not describe the exact nucleotide sequence of SEQ ID NO:2 of the current invention. Instead, Erickson discloses the full length Her-2/neu sequence (see NCBI Accession No. AX060704, cited in First Supplemental Information Disclosure submitted herewith as **NPL1**). The full length sequence described in Erickson is 3768 base pairs in length. The Erickson sequence includes the intracellular domain of Her-2/neu, which is not part of the claimed invention. In contrast, the current application discloses a pharmaceutical composition comprising a *C-terminally truncated* Her-2/neu sequence. One embodiment described in the specification is a pharmaceutical composition wherein the nucleotide sequence encoding a truncated human Her-2/neu protein comprises SEQ ID NO:2, which is 2052 base-pairs in length. In contrast, Erickson does not describe SEQ ID NO:2 or any other C-terminally truncated Her-2/neu nucleotide sequence recited in the claims. Specifically, Erickson in combination with Lee 1 and/or Lee 2 is

structurally distinguishable from pCK_{TM}, $pTV2_{TM}$, $pCK_{TM\text{-}GMCSF}$, contrary to the Examiner's assertion. *See* Office Action, page 20. Further, Erickson does not describe the C-terminally truncated Her-2/neu of the invention and an adjuvant for use as a DNA vaccine. Thus, the combination of Erickson with the other references cited by the Examiner does not predict the compounds or methods of the claimed invention.

Chen describes pNeu expression vectors encoding full-length *rat* neu cDNA ($pNeu_N$), neu extracellular domain ($pNeu_E$) and neu extracellular domain and transmembrane domain ($pNeu_{TM}$). In contrast, the claimed invention is directed to a nucleotide sequence encoding a C-terminally truncated *human* Her-2/neu protein. The human Her-2/neu nucleotide and amino acid sequences are different than the rat Her-2/neu nucleotide and amino acid sequences. Thus, Chen in combination with Lee 1 and/or Lee 2 is structurally distinguishable from pCK_{TM}, $pTV2_{TM}$, $pCK_{TM\text{-}GMCSF}$, contrary to the Examiner's assertion. *See* Office Action, page 20.

Although Chen showed protective immunity against Tg1-1 tumor cells in mice injected with pNeu plamids, Chen did not detect anti-neu antibodies in the majority of the $pNeu_E$ and $pNeu_{TM}$ mice even after co-injection with pIL-2. As noted above, Piechocki, published after Chen, teaches that there is still some debate as to which epitopes are most important for tumor rejection in murine and human models and the way in which to best present these antibodies to the immune system for effective priming. Taking the references as a whole, a person of ordinary skill in the art would not view the rat constructs described in Chen, which did not induce significant antibody induction, predictive of a pharmaceutical composition that includes a nucleotide sequence encoding a C-terminally truncated *human* Her-2/neu protein, said protein *consisting* of a signal peptide, the entire extracellular domain

and transmembrane domain of Her-2/neu or a signal peptide and the entire extracellular domain of Her-2/neu; and an *adjuvant*. Piechocki shows that uncertainty regarding the specific Her-2/neu epitopes necessary for an effective human Her-2/neu DNA vaccine was not resolved by the study of the rat neu gene in Chen. Chen does not describe the human Her-2/neu constructs of the claimed invention or overcome the deficiencies in Piechocki with regard to the unpredictability of the human Her-2/neu epitopes or the prediction by Piechocki that additional epitopes may be necessary for an effective human Her-2/neu DNA vaccine. Thus, a person of ordinary skill in the art at the time of the invention would not have predicted the compositions or methods of the claimed invention.

Lee 1 discloses a pCK expression vector that is able to drive high levels of $VEGF_{165}$ gene expression in the skeletal muscles of mice. Lee 2 discloses a pTV expression vector used for gene expression of hepatitis C virus (HCV) envelope genes without and with GM-CSF gene. Lee 1 and Lee 2 do not describe a pTV2 or pCK expression vector that includes a tumor associated gene, in particular a gene encoding a C-terminally truncated Her-2/neu. Applicants assert that the plasmid construct of the invention was not predictable in view of the cited references, especially in view of the numerous potential combinations of vectors and genes of interest that could be envisioned. Lee 1 provides no disclosure using the pCK vector with nucleotide sequences other than $VEGF_{165}$. Lee 2 provides no disclosure for use of the pTV2 vector with nucleotide sequences other than HCV envelope genes and GM-CSF. Neither Lee 1 or Lee 2 predict use of the pTV2 or pCK expression vector for expression of DNA vaccines for the treatment and/or prevention of cancer. Applicants assert that the plasmid construct of the invention was not predictable in view of the cited references, especially due to the numerous potential vectors that could be envisioned and a lack of

disclosure to support selection of the pTV2 or pCK vectors for expression of the C-terminally truncated Her-2/neu gene of the current invention.

Bocchia is a review article that discusses anti-tumor vaccination. The article includes a general discussion of DNA vaccines. Bocchia does not describe use of the specific pharmaceutical composition of the claimed invention. Nor does Bocchia predict which human Her-2/neu epitopes that may be necessary for an effective human Her-2/neu DNA vaccine. Bocchia does not overcome any of the deficiencies of the other combined references cited by the Examiner or predict the effect of the pharmaceutical composition, let alone the methods of the claimed invention.

The combined references cited by the Examiner do not predict the pharmaceutical composition or methods of the current invention. In addition, the specification describes surprising and unexpected results in that the C-terminally truncated human Her-2/neu protein of the current invention is able to illicit CTL response, which is known to be important for effective anti-tumor immunity. The disclosure of the human Her-2/neu C-terminally truncated construct of the claimed invention in combination with an adjuvant that induces antibody *and* CTL responses, and is effective in both preventative and therapeutic models, is an improvement over the Her-2/neu constructs cited by the examiner.

Deficiencies in the references cited by the Examiner are discussed above. A person of ordinary skill in the art would not predictably arrive at the claimed invention upon combination of the references, especially given the unpredictability in the art and teachings cited by the Examiner. Therefore, Applicants respectfully request withdrawal of the rejection as it relates to the currently pending claims.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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